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Rana AQ, Saeed U, Rana AN. Role of Environmental Factors in Cryptococcal Meningitis in Immunocompetent Individuals. Acta Neurol Belg 2014; 114(1):75–76 DOI 10.1007/s13760-013-0193-7

Role of Environmental Factors in Cryptococcal Meningitis in Immunocompetent Individuals

Abdul Qayyum Rana [1] • Usman Saeed [1, 2] • Afshan N. Rana

[1] Parkinson's Clinic of Eastern Toronto & Movement Disorders Center, Toronto, ON, Canada
[2] University of Toronto – Department of Biological Sciences, Toronto, ON, Canada
Correspondence**:** Dr. Abdul Qayyum Rana; E-mail: ranaaq@yahoo.com

To the Editor-in-Chief,

Cryptococcal Meningitis (CM) is caused by members of the yeast species, *Cryptococcus neoformans.* Although *C.neoformans* can cause infection in any part of the body, the fungus prefers to invade regions of the lungs and CNS [1]. The infection is thought to be acquired through the respiratory tract, and reaches the meninges through the blood circulation [1]. Symptoms of CM include headaches, malaise, fever, and changing psycho-mental stability. CM is most commonly recognized as an opportunistic infection in immunocompromised individuals, especially those suffering from HIV/AIDS, liver cirrhosis or sarcoidosis [2]. Hence, CM risk is usually overlooked or totally ignored during the differential diagnosis of immunocompetent individuals who present meningitis like symptoms. Recent reports have indicated rising prevalence of CM in individuals who are *believed* to be immunocompetent, resulting in delayed or misdiagnosis of such patients [3]. Other factors are emerging to be important determinants when diagnosing a patient with meningitis like symptoms. Such factors include environmental factors originally believed to be important in Africa or in tropical environments. Environmental factors (as they relate to CM) can be defined as any factor originating from the environment that results in immunodeficiency, either by a significant decrease in white blood cells count or by interfering with normal immunological response of the body.

A 45-year old male was presented to the emergency department with severe headaches, dizziness, and progressive loss of consciousness. Lumbar puncture results indicated a white blood cell count of 121 (70% neutrophils, 20% lymphocytes). Blood glucose level was measured to be 3.4 mmol/L and the protein level in CSF was found to be 1.89 g/L. Bacterial gram stain and culture were negative. The India ink stain for cryptoccocus was *not* performed as CM was not considered in the differential diagnosis of the patient. The patient was intubated because he had developed laboured breathing. Acyclovir and a triple coverage of ceftriaxone, vancomycin and ampicillin were started for herpes encephalitis and bacterial meningitis respectively. The patient's medical history revealed that he was a smoker, but a healthy individual with no history of alcoholism, liver diseases, sarcoidosis or any other CM related physiological risk factors. Although there was no acute exposure to carbon monoxide, the patient started a new job two month prior to admission to

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the hospital. The work involved working in a fairly confined dusty space with a propane powered forklift. He had not travelled elsewhere, and all other family members at home were healthy. The physical examination of the patients showed that both pupils were non-reactive to light. Corneal reflexes, nasal tickles and oculocephalic reflexes were absent. Spontaneous movements of the limbs or in response to pain were also absent. A review of MRI and CAT scans indicated progressive cerebral edema (Figure 1 & Figure 2). HIV, VDRL and active TB tests were negative. Several days later, results from CSF indicated the presence of cryptococcal antigen, suggesting that the patient had CM. Subsequently, the patient was treated with Amphotericin B. Unfortunately, the treatment was unsuccessful and he passed away approximately a week after.

This case highlights the importance of considering environmental factors (besides known risk factors) during the diagnosis of a patient presented with meningitis like symptoms. Our patient worked in a fairly confined space with possible chronic exposure to dust, industrial chemicals and toxins for two month prior to admission to the hospital. Working in a confined, unventilated and noisy industrial place can expose a person to increased anxiety which negatively impacts the immune system. Dust found in industrial setting contains harmful microscopic particles, microbacteria and traces of heavy metals that can result in severe allergic responses and inhibits immune cell proliferation. Smoking inhibits the cilia found in lungs and suppresses the immune system by inhibiting T-cell and cytokines production. Exposure to industrial chemicals, such as propane, benzene, halogenated aromatic hydrocarbons and dioxins, can cause significant immunocompression. Our patient may have experienced some or all of the above listed environmental factors that caused significant immunocompression to the extent that he developed CM infection upon fungal exposure. Such environmental factors associated with CM infections are traditionally given more importance in African countries, where epidemics occur throughout Africa in the dry season, coinciding with periods of very low humidity and dusty conditions, and disappear with the onset of the rains [4]. On the contrary, this case study highlights the fact that any environmental factor capable of suppressing immune system can potentially cause CM infections in a patient, regardless of geographical boundaries. We recommend more studies to test this hypothesis.

In recent years, it has been noted that another primary difficulty in treating immunocompetent CM patients is delayed diagnosis. Since the diagnosis of CM is confirmed by CSF culture, it is essential to maximize the sensitivity and specificity of CSF culture to swiftly identify CM infection. CSF culture and antigen tests may be negative in immunocompetent patients with CM infections. On a more positive note, CM diagnosed immunocompetent patients display better clinical outcomes and anti-fungal drugs such as, Amphotericin B and Fluconazole, are administered to treat CM patients [5]. Due to delayed diagnosis, our patient was not successfully responsive to Amphotericin B treatment, which proved to be fatal. Early diagnosis of CM can prevent the fatality and disability that can result from untreated CM.

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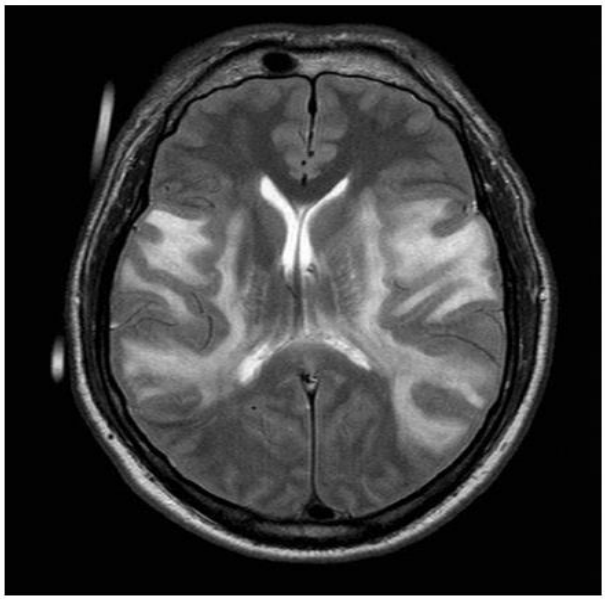

Figure 1:
MRI brain axial view T2 image above showing bilateral frontoparietal hyperintense signal, compression of both lateral ventricles, mild right sided shift and diffuse vasogenic brain edema.

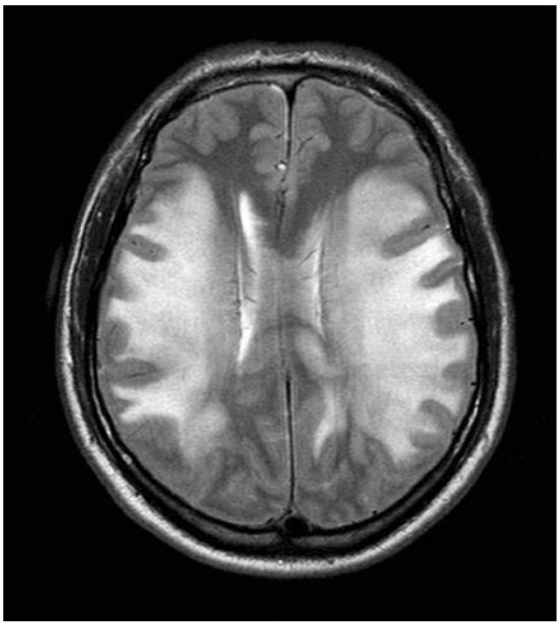

Figure 2: MRI brain axial view T2 image above showing bilateral fronto-parieto-occipital hyperintense signal consistent with diffuse vasogenic brain edema.

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